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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional): 00-0193US02

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Application Number	Filed
10/798,592	March 11, 2004

First Named Inventor: Robert A. Herrmann

Art Unit	Examiner
1611	Isis A.D. Ghali

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

- [ ] applicant /inventor.
- [ ] assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)
- [x] attorney or agent of record. Registration number 29,674
- [ ] attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34.

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NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

[x] *Total of 1 forms are submitted.

REASONS FOR REQUESTING PRE-APPEAL REVIEW

1) Status of the Claims

Claims 1-41 are pending in the application. Claims 23-39 were previously withdrawn from consideration pursuant to a restriction requirement. Thus, Claims 1-22 and 40-41 are presented for pre-appeal review.

2) Rejection Under 35 USC § 103(a) Over STAMLER and SOGO

Claims 1-22, 40-41 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Stamler et al, U.S. Patent No. 6,087,479 (STAMLER) in combination with the article, Sogo et al, "S-Nitrosothiols cause prolonged, nitric oxide mediated relaxation in human saphenous vein and internal mammary artery: therapeutic potential in bypass surgery" (SOGO). This rejection is in error.

The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. MPEP 2141. " '[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.' " *KSR International Co.* v. *Teleflex Inc.*, 550 U.S. ___, 82 USPQ2d 1385 (2007), quoting *In re Kahn* , 441 F.3d 977, 988, (Fed. Cir. 2006). It should be noted that the prior art reference (or references when combined) must teach or suggest all the claimed features. "When determining whether a claim is obvious, an examiner must make 'a searching comparison of the claimed invention – *including all its limitations* – with the teaching of the prior art.' … Thus, 'obviousness requires a suggestion of all limitations in a claim.' …" *Ex parte Wada and Murphy*, BPAI Appeal No. 2007-3733, January 14, 2008 (emphasis in original) (citations omitted). In addition, there must be a reasonable expectation of success. See MPEP 2143.02.

Moreover, rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness. *In re Kahn,* 441 F.3d 977, 988 (Fed. Cir. 2006), *cited with approval in, KSR Int'l v. Teleflex, Inc.*, 127 S. Ct. 1727, 1740-41, 82 USPQ 1385, 1396 (2007). As explained below, none of the references alone or in combination provides any reason or suggestion to combine the references to arrive at the present invention. *In re Nilssen*, 851 F2d. 1401, 1403, 7 USPQ2d 1500, 1502 (Fed. Cir. 1988).

Claim 1 provides:

A medical article comprising:

a first polymer matrix having a first nitric oxide donor compound disposed within the first polymer matrix;

a second polymer matrix having a second nitric oxide donor compound disposed within the second polymer matrix, said second nitric oxide donor compound differing from said first nitric oxide donor compound, and the first polymer matrix being chemically distinct from the second polymer matrix;

wherein said medical article is adapted, after placement at a delivery position on or within the body of a patient, for local delivery of said first nitric oxide donor compound and a nitric

oxide product of said first nitric oxide donor compound and for local delivery of said second nitric oxide donor compound and a nitric oxide product of said second nitric oxide donor compound.

In contrast to the medical article of Claim 1 of the present invention, STAMLER provides the following:

> A method for preventing adverse effects associated with the use of a medical device in a patient by introducing into the patient a device of which at least a portion includes a prophylactic or therapeutic amount of a nitric oxide adduct. The nitric oxide adduct can be present in a matrix coating on a surface of the medical device; can be coated per se on a surface of the medical device; can be directly or indirectly bound to reactive sites on a surface of the medical device; or at least a portion of the medical device can be formed of a material, such as a polymer, which includes the nitric oxide adduct.

(Abstract, emphasis added).

The Examiner agrees that STAMLER does not explicitly teach "including two different nitric oxide donors in the same device" (emphasis added) but notes that STAMLER includes "two nitric oxide donors in [a] single device in different portions, e.g. device itself and its coating." (Office Action, 11/17/09, page 4, emphasis added). With regard to the later quotation, it is to be kept in mind that the "two nitric oxide donors" in STAMLER referred to by the Examiner are the same and are *not* different from one another. The Examiner also takes the position that STAMLER discloses "that the material of the medical device [is] different from the coating matrix." (Office Action, 11/17/09, page 3).

It is important to note that STAMLER does not teach or suggest a medical article comprising *a first polymer matrix having a first nitric oxide donor compound disposed within the first polymer matrix; a second polymer matrix having a second nitric oxide donor compound disposed within the second polymer matrix, said second nitric oxide donor compound differing from said first nitric oxide donor compound.* It is clear that one nitric oxide adduct is contemplated. While STAMLER lists using the nitric oxide adduct in possible combination with another ingredient, the mention of additional ingredients does not include additional nitric oxide adducts. (See STAMLER at col. 4, line 14; and col. 5 line 66-col. 6, line19). If STAMLER had intended adding a second and different nitric oxide donor, it is respectfully submitted that such an option would have been stated in STAMLER, especially since combinations with other active agents are described. For the same reason, STAMLER also does not teach or suggest a medical article *adapted, after placement at a delivery position on or within the body of a patient, for local delivery of said first nitric oxide donor compound and a nitric oxide product of said first nitric oxide donor compound and for local delivery of said second nitric oxide donor compound and a nitric oxide product of said second nitric oxide donor compound* since these nitric oxide donors in the present invention have been described as being chemically different.

It is also maintained by the Applicant that STAMLER's listing of alternative strategies is not sufficient to support the Examiner's interpretation of STAMLER as describing the simultaneous inclusion

of a nitric oxide donor in the device itself and in a coating on the device. For example, in the Abstract, STAMLER states (emphasis added) (noting use of the singular term "adduct"):

> The nitric oxide adduct can be present in a matrix coating on a surface of the medical device; can be coated per se on a surface of the medical device; can be directly or indirectly bound to reactive sites on a surface of the medical device; ***or*** at least a portion of the medical device can be formed of a material, such as a polymer, which includes the nitric oxide adduct.

Nowhere in STAMLER is it taught or suggested to employ first and second chemically distinct polymer matrices, *each having a nitric oxide donor disposed therein*, especially when two different nitric oxide doors are used. It is also again noted that the Examiner has previously agreed that STAMLER does not teach including two different nitric oxide donors in the same device. (Office Action, 11/17/09, page 4). Thus, STAMLER does not teach or suggest two different NO donors, much less two different NO donor in two separate matrices.

The Examiner then turns to SOGO stating that SOGO teaches the "administration of two different nitric oxide donors simultaneously" (Office Action, page 4). It is respectfully submitted that the Examiner has misinterpreted SOGO.

SOGO describes a study of the performance of certain S-nitrosothiols in causing prolonged, nitric oxide-mediated relaxation in human saphenous vein and internal mammary artery for by-pass surgery. SOGO also describes the preparation of test tissue (in the form of rings of tissue) and the suspension of the tissue samples in an organ bath. (See page 1237, col.2). In the experimental protocol section of SOGO it is recited that four NO donor drugs were selected for testing: (1) N-(S-nitroso-N-acetylpenicillamine)-2-amino-2-deoxy-1,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose (RIG200), (2) S-nitrosoglutathione (GSNO), (3) glyceryl trinitrate (GTN) and (4) sodium nitroprusside (SNP) (see page 1237), two of which are S-nitrosothiols.

It is important to note that SOGO does not describe the administration of two different nitric oxide donors simultaneously. More particularly, in the experimental protocol section SOGO states that "[e]ach ring was randomly allocated to treatment with increasing concentrations . . . of either RIG200, GSNO, SNP or GTN in organ baths, and was treated with each concentration of drug until the relaxation reached plateau . . ." (see page 1237) (emphasis added). Thus, the testing in SOGO was done by using one drug serially in various concentrations. Nowhere in SOGO is described any combination of NO donor compounds. Rather SOGO presents the drugs, for example, nitrosoglutathione and N-(S-nitroso-N-acetylpenicillamine) as alternatives, rather than as a combination.[1] There is no description of two or more different drugs being tested on the same tissue simultaneously.

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[1] In addition to the preceding evidence, see further the experimental results in Sogo et al., in which response curves for RIG200 (N-(S-nitroso-N-acetylpenicillamine) are *separate and distinct* from response curves for GSNO (nitrosoglutathione) and there are no data or textual support for a combination of two or more NO donor compounds. (*See* Figures 3, 4, 5, 6, and their accompanying text.)

The Examiner's statement that SOGO "recognized and suggested administration of two different nitric oxide donors simultaneously to improve more than one function in coronary patients" (Office Action, 11/17/09 page 8; and see also the Advisory Action) is simply not supported in the text of SOGO. There is nothing in SOGO which teaches or suggests the administration of two different nitric oxide donors simultaneously, nor is there anything in SOGO that suggests that donors referred to by the Examiner provide more than one function.

In this regard, according to the final Office Action and the Advisory Action, Sogo teaches the advantages of two specific NO adducts (i.e., S-nitroso-N-acetyl-D,L-penicillamine and S-nitrosoglutathione) in treating "vascular diseases." However, as a first point, it is noted that while SOGO describes S-nitrosoglutathione (GSNO), it does not describe S-nitroso-N-acetyl-D,L-penicillamine, but rather describes a different compound: N-(S-nitroso-N-acetylpenicillamine)-2-amino-2-deoxy-1,3,4,6-tetra-O-acetyl-b-D-glucopyranose (RIG200).

Moreover, it is noted that SOGO teaches that the NO compounds are useful for the same purpose—bypass grafting for treatment of coronary disease. More particularly, SOGO teaches the NO compounds can be used to inhibit vasospasm in human saphenous vein (SV) and internal mammary artery (IMA) grafts after implantation by incubation of the vessels with the NO compounds (so as to avoid the need for high pressure distention or papaverine treatment, normally used to overcome spasm, which can cause damage to the endothelium and may compromise patency) (SOGO, page 1243). There is no teaching or suggestion in SOGO, however, that one having ordinary skill in the art "would use these two adducts together for the advantage taught by SOGO [i.e., inhibiting vasospasm]" as alleged by the Examiner. Indeed, SOGO teaches that RIG200 is likely superior to GSNO for the purposes taught therein (SOGO, page 1241). Consequently, contrary to the Examiner's assertion, one having ordinary skill in the art aware of the device taught by STAMLER would ***not*** have been "motivated to incorporate one NO [donor] in the coating and replace the active agent incorporated in the device itself with the other NO [donor] taught by Sogo". Indeed, one would not have been motivated to provide the NO compounds of SOGO in a medical device at all, but rather would have been motivated to apply a single compound directly to tissue.

Further, with regard to the Examiner's assertion that it is well known that it is prima facie obvious to combine two or more ingredients each of which is taught by the prior art to be useful for the same purpose[2] in order to form a third composition which is useful for the same purpose, ***at best***, it would be obvious to combine the RIG200 and GSNO of SOGO for the purpose of inhibiting vasospasm in human SV and IMA grafts after implantation. However, this purpose is not the same as that of STAMLER (preventing adverse effects associated with the use of a medical device in a patient). Thus the artisan would not have been motivated to provide the two NO adducts taught by SOGO into a single device.

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[2] Note that this is contrary to the Examiner's assertion that the GSNO and GIG200 of SOGO provide *different functions*.

Moreover, the preceding citation indicates that it is prima facie obvious to combine two or more ingredients in a single *composition*, whereas in Applicant's claims, the different NO donors are provided in *different* compositions (i.e., first and second matrices). Clearly, "one having ordinary skill in the art aware of the device taught by Stamler" would ***not*** have been "motivated to incorporate one NO [donor] in the coating and replace the active agent incorporated in the device itself with the other NO [donor] taught by Sogo" as alleged by the Examiner.

Again, STAMLER does not teach or suggest the concurrent use of two different NO donors, much less two different NO donor in two separate matrices. Indeed, STAMLER does not even describe the use of a *single* nitric oxide donor in separate matrices as claimed. While STAMLER teaches that the nitric oxide adduct can be applied in combination other therapeutic agents such as anti-thrombogenic agents, STAMLER does not teach or suggest administering the nitric oxide adduct and the second therapeutic agent from chemically distinct polymeric matrixes as claimed; instead, as noted in the Office Action, 11/17/09, at page 6, the "second therapeutic agent that has anti-thrombogenic effect is provided along with NO adduct in the coating [i.e., in the same matrix] or linked to the reactive sites in or on the body of the device [i.e., not in a matrix at all]."

Like STAMLER, SOGO does not teach or suggest the concurrent use of two different NO donors, nor does SOGO teach or suggest the use of *any* polymeric delivery system, much less two different NO donor in two separate matrices. SOGO as the secondary reference thus does not remedy the deficiencies in STAMLER. Specifically, SOGO does not teach or suggest first and second chemically distinct polymer matrices, each having a different nitric oxide donor disposed therein. Nor does SOGO teach or suggest administration of two different nitric oxide donors to the same tissue.

Any combination of STAMLER and SOGO is merely based on the use of undue hindsight, which is prohibited. *See Akso N.V. v. U.S. International Trade Commission*, 808 F.2d 1241, 1480-81, 1 U.S.P.Q.2d, 1241, 1246 (Fed. Cir. 1986), *cert. denied,* 482 U.S. 909 (1987), *Loctite Corp. v. Ultraseal Ltd.*, 781 F.2d 861, 874, 228 U.S.P.Q. 90-99 (Fed. Cir. 1985). Also see MPEP § 2142, second paragraph. The combination is based upon *applicant's own disclosure*, rather than the teachings within the four corners of SOGO and STAMLER. Even if combined, such combination of SOGO and STAMLER does not produce the current invention.

In light of the above remarks, withdrawal of this rejection of the claims under 35 U.S.C. § 103 is respectfully requested.